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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
RAMIREZ, DELIA M	

ART UNIT	PAPER NUMBER
1652	

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11

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/963,668	RIEPING ET AL.	
	Examiner	Art Unit	
	Delia M. Ramirez	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) *8 and 10-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7 and 9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 September 2001* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the Application

Claims 1-27 are pending.

Applicant's election without traverse of Group I, claims 1-7 and 9, partially drawn to a fermentation process for the production of L-amino acids which use a microorganism from the Enterobacteriaceae family wherein said organism contains a defective pckA gene, in Paper No. 10, filed on 7/16/2003 is acknowledged.

Claims 8, 10-27 are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Specification

1. The specification is objected to because of the presence of a blank space in page 33. Appropriate correction is required.

2. The specification is objected to since it fails to follow the specification layout guidelines as provided in 37 CFR 1.77(b). Applicants are reminded that the Brief Description of the Drawings should be placed between the Brief Summary of the Invention and the Detailed Description of the Invention. Appropriate correction is required.

Priority

3. Acknowledgment is made of a claim for domestic priority under 35 U.S.C. 119(e) to provisional application No. 60/237,610 filed on 10/04/2000.

4. Acknowledgment is made of a claim for foreign priority under 35 U.S.C. 119(a)-(d) to GERMANY DE 100 48 605.3 filed on 09/30/2000, GERMANY DE 100 55 516.0 filed on 11/09/2000, and GERMANY DE 101 30 192.8 filed on 06/22/2001.

Information Disclosure Statement

5. The information disclosure statement (IDS) submitted on 6/21/2002 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Drawings

6. The drawings have been reviewed and are objected under 37 CFR 1.84 or 1.152. See attached Notice of Draftsperson's Patent Drawing Review. Applicant is required to submit the drawing corrections within the time period set in the attached Office communication. See 37 CFR 1.85(a). Failure to take corrective action within the set period will result in ABANDOMENT of the application. In addition, if amendments to the specification are needed due to drawing corrections, Applicant is requested to submit such amendments while the case is being prosecuted to expedite the processing of the application.

Claim Objections

7. Claim 1 is objected because of the following informalities: for clarity, it is suggested that the term "Fermentation process" be replaced with "A fermentation process". Appropriate correction is required.

8. Claims 2-7 and 9 are objected to because of the following informalities: for clarity, it is suggested that the term "Process according to claim" be replaced with "The process according to claim". Appropriate correction is required.

9. Claim 9 is objected to because said claim is still partially drawn to a non-elected invention, i.e. the invention of claim 8. Examination of such claim will be restricted to the subject matter elected. Appropriate correction is required.

Claim Rejections - 35 USC § 112, Second Paragraph

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 1-7 and 9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

12. Claim 1 (claims 2-7 and 9 dependent thereon) is indefinite in the recitation of "process for the preparation of L-amino acids, especially L-threonine.." as it is unclear if the term "especially threonine" is limiting the process to the preparation of L-threonine only. For examination purposes, it will be assumed that the claim is directed to a fermentation process for the preparation of any L-amino acid. Correction is required.

13. Claim1 (claims 2-7 and 9 dependent thereon) is indefinite in the recitation of "fermentation of the microorganisms of the family ..." due to the lack of antecedent basis for the microorganisms. Correction is required.

14. Claim 1 (claims 2-7 and 9 dependent thereon) is indefinite in the recitation of "in which microorganisms at least the pckA gene or nucleotide sequences coding therefor are attenuated and, in particular switched off" for the following reasons. First, the meaning of the term "in which microorganisms at least the pckA gene " is unclear. Furthermore, it is unclear as to how a nucleotide sequence can be attenuated or switched off since a sequence is a graphical representation of the order in which nucleotides/amino acids are arranged in a molecule. In addition, it is unclear if the term "in particular, switched off" if further limiting the claim. For examination purposes, it will be assumed that the term's meaning is "wherein the endogenous pckA gene of said microorganisms is attenuated". It is noted that the definition of attenuation used in the interpretation of the claim is that disclosed in the specification (page 2, line 25, page 3, line 2). Correction is required.

15. Claim 1 (claims 2-7 and 9 dependent thereon) is indefinite in the recitation of "enrichment of the L-amino acid in the medium" as it is unclear and confusing. For examination purposes, it will be assumed that step (b) refers to concentration of the fermentation broth to eliminate water and increase the concentration of L-amino acids in the broth. Correction is required.

16. Claim 1 (claims 2-7 and 9 dependent thereon) is indefinite in the recitation of "isolation of the L-amino acid, constituents of the fermentation broth and the biomass in its entirety or portions thereof optionally being isolated as a solid product together with the L-amino acid" for the following reasons. As written, it is unclear if the term "optionally being isolated as a solid product..." is further limiting the claim. Furthermore, the term "solid product" is redundant since biomass is a solid product. For examination purposes, the term will be interpreted as

"isolation of the L-amino acid, constituents of the fermentation broth and biomass". Correction is required.

17. Claims 1, 4, and 5 (claims 2-3, 6-7 and 9 dependent thereon) are indefinite in the recitation of "pckA". While the gene nomenclature used may be appropriate for some organisms such as E. coli, the use of this nomenclature for genes encoding proteins of identical function in other organisms may not be accurate. As known in the art, genes encoding proteins of identical function in two different organisms may use different designations. For example, the ARO4 gene of Candida albicans encodes a DAHP synthase whereas the E. coli counterpart is the aroF gene. See the abstract of Sousa et al. (Microbiology 148(Pt5):1291-1303, 2002). As such, the use of gene terminology which is applicable to some organisms and not to others is confusing since the claims use this gene nomenclature with respect to any organism. If Applicants wish to keep the terminology used, it is suggested that the corresponding protein be recited in the claim. For examination purposes, the terms will be interpreted as "gene encoding phosphoenolpyruvate (PEP) carboxykinase". Correction is required.

18. Claim 4 is indefinite in the recitation of "wherein the expression of the polynucleotide(s) coding for the pckA gene is attenuated and, in particular, switched off" for the following reasons. First, there is no antecedent basis for the "polynucleotide(s) coding for the pckA gene". Furthermore, one cannot determine if the term "in particular, switched off" is further limiting the claim. For examination purposes, the term will be interpreted as "wherein the expression of the pckA gene is attenuated". Correction is required.

19. Claim 5 is indefinite in the recitation of "polypeptide (enzyme protein) coded for by the polynucleotide pckA" due to the lack of antecedent basis for the term "polynucleotide pckA".

For examination purposes, it will be assumed that the term's meaning is "polypeptide encoded by the pckA gene". Correction is required.

20. Claims 6-7 are indefinite in the recitation of "genes selected from the group comprising" since the term "comprising" implies other genes in the group which are not recited in the claims. As such, one cannot determine the full scope of the claims. It is suggested that the term "comprising" be replaced with "consisting of". Correction is required.

21. Claims 6-7 are indefinite in the recitation of "in particular, overexpressed" or "in particular, switched off" as it is unclear if the terms are further limiting the claims. For examination purposes, no patentable weight will be given to such terms. Correction is required.

Claim Rejections - 35 USC § 112, First Paragraph

22. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

23. Claims 1-7 and 9 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 4 and 5 are directed to a fermentation process for the production of a genus of L-amino acids wherein said process uses any Enterobacteriaceae microorganism comprising a genus of PEP carboxykinase genes which have been modified in any way such that the

intracellular activity of the PEP carboxykinase is reduced or eliminated. See claim interpretation in Claim Rejections under 35 USC 112, second paragraph. Claim 2 is directed to the process of claim 1 as described above with the added limitation that other genes from any source involved in the biosynthetic pathway of the desired L-amino acid can be amplified. Claim 3 is directed to the process of claim 1 with the added limitation that the metabolic pathways which reduce the formation of the desired L-amino acid are partially switched off in the Enterobacteriaceae microorganism used. Claim 6 is directed to the process of claim 1 with the added limitation that genes from any source, as recited in the claims, be amplified in any way. Claim 7 is directed to the process of claim 1 with the added limitation that selected Enterobacteriaceae genes, as recited in the claim, are modified in any way such that the intracellular activity of the corresponding polypeptides is reduced or eliminated. Claim 9 is directed to the process of claim 1 with the added limitation that the L-amino acid produced is L-isoleucine, L-valine, L-lysine, or L-threonine.

While the specification discloses the structure of the E. coli pckA gene, there is no disclosure of other PEP carboxykinase genes isolated from other microorganisms. Similarly, while the E. coli thrABC operon, pyc, pps, ppc, pntA, pntB, rhtB, rhtC, gdhA, tdh, mdh, yjfA and ytfP genes are either known in the art or disclosed by Applicants, there is no disclosure in the specification of similar genes isolated from other microorganisms, nor there is disclosure of the critical structural elements required in a polynucleotide to encode the proteins corresponding to the genes recited above. Furthermore, the specification only discloses the production of L-threonine, L-isoleucine, L-valine and L-lysine with an E. coli cell which comprises an inactivating deletion in the E. coli pckA gene. Thus, in addition to the lack of disclosure of other

PEP carboxykinase genes, no disclosure has been made of the production of other L-amino acids, the use of other Enterobacteriaceae microorganisms, or other modifications which result in the reduction or elimination of PEP carboxykinase activity. Also, while the specification discloses production of L-threonine, L-lysine, L-isoleucine, or L-valine with an E. coli cell wherein said cell comprises an E. coli pckA gene which contains an inactivating deletion and wherein the E. coli gdhA gene is overexpressed, the E. coli rhtC gene is overexpressed, the E. coli thrABC operon is overexpressed, the E. coli tdh gene contains an inactivating deletion, or the E. coli ytfP-yjfA gene region contains an inactivating deletion, the specification fails to disclose (1) other genes isolated from other organisms which are part of other biosynthetic pathways as recited in the claims that can be amplified and would result in production of any L-amino acid, (2) how to amplify the intracellular activity of the gene products other than by increasing the copy number of the gene or using a strong promoter, (3) other genes related to metabolic pathways which reduce the formation of the desired L-amino acid, and (4) how to modify the genes described in (2) such that their expression is partially switched off.

The argument can be made that the genera of genes and modifications required to practice the claimed method are adequately described since one can isolate these genes by structural (i.e. sequence) comparison using the information disclosed in the instant application or the prior art. However, the state of the art teaches that sequence comparison alone should not be used to determine function and that small structural changes can drastically change function. Bork (Genome Research, 10:398-400, 2000) teaches protein function is context dependent, and both molecular and cellular aspects must be considered (page 398). Witkowski et al. (Biochemistry 38:11643-11650, 1999) teaches that one amino acid substitution transforms a β-

ketoacyl synthase into a malonyl decarboxylase and completely eliminates β-ketoacyl synthase activity. Van de Loo et al. (Proc. Natl. Acad. Sci. 92:6743-6747, 1995) teaches that polypeptides of approximately 67% homology to a desaturase from *Arabidopsis* where found to be hydroxylases once tested for activity. Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001) teaches that two naturally occurring Pseudomonas enzymes having 98% amino acid sequence identity catalyze two different reactions: deamination and dehalogenation, therefore having different function. Broun et al. (Science 282:1315-1317, 1998) teaches that as few as four amino acid substitutions can convert an oleate 12-desaturase into a hydrolase and as few as six amino acid substitutions can transform a hydrolase to a desaturase. The specification only discloses a few species of the genera of genes and gene modifications which is insufficient to put one of ordinary skill in the art in possession of all attributes and features of all species within the genera required to practice the claimed method. Thus, one skilled in the art cannot reasonably conclude that Applicant had possession of the claimed invention at the time the instant application was filed.

24. Claims 1-7 and 9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (1) a fermentation process for the preparation of L-threonine, L-lysine, L-isoleucine or L-valine using an E. coli cell which comprises the E. coli pckA gene containing an inactivating deletion, (2) the process of (1) wherein the E. coli cell further comprises the E. coli tdh gene containing an inactivating deletion, (3) the process of (1) wherein the copy number of the E. coli gdhA gene, rhtC and/or thrABC genes is increased or wherein said E. coli genes are placed under the control of a strong promoter, (4) the process of

(1) wherein the E. coli cell further comprises an inactivating deletion in the E. coli ytfP-yjfA gene region, does not reasonably provide enablement for (1) a fermentation process for the production of any L-amino acid using any Enterobacteriaceae microorganism wherein said microorganism comprises any PEP carboxykinase gene which have been modified in any way such that the intracellular PEP carboxykinase activity is reduced or eliminated, (2) the process of (1) wherein any gene associated with a biosynthetic pathway of the desired L-amino acid is amplified in any way, (3) the process of (1) wherein any gene associated with a metabolic pathway which reduces the formation of the desired L-amino acid is partially switched off in any way, (4) the process of (1) wherein any thrABC operon, pyc, pps, ppc, pntA, pntB, rhtB, rhtC or gdhA gene is amplified in any way, (5) the process of (1) wherein any Enterobacteriaceae tdh, mdh, yjfA or ytfP gene is modified in any way to reduce or eliminate the intracellular activity of its gene product. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The criteria for undue experimentation, summarized in *re Wands*, 8, USPQ2nd 1400 (Fed. Cir. 1988) are: 1) quantity of experimentation necessary, 2) the amount of direction or guidance presented, 3) the presence and absence of working examples, 4) the nature of the invention, 5) the state of prior art, 6) the relative skill of those in the art, 7) the predictability or unpredictability of the art, and 8) the breath of the claims.

The scope of the claims, as described above, is not commensurate with the enablement provided in regard to the large number of unknown genes and gene modifications required to practice the claimed method. As indicated above, the specification and/or the prior art discloses

the structure of the E. coli pckA, thrABC operon, pyc, pps, ppc, pntA, pntB, rhtB, rhtC, gdhA, tdh, mdh, yjfA and ytfP genes but there is no disclosure in the specification of similar genes isolated from other microorganisms, nor there is disclosure of the critical structural elements required in a polynucleotide to encode the proteins corresponding to the genes recited above. Furthermore, the specification fails to disclose (1) the production of other L-amino acids with the exception of L-isoleucine, L-threonine, L-valine and L-lysine, (2) the use of other Enterobacteriaceae microorganisms with the exception of E. coli, (3) the structure or identity of other genes isolated from other organisms which are part of other biosynthetic pathways as recited in the claims that can be amplified and would result in production of any L-amino acid, (4) how to amplify the intracellular activity of the gene products of (3) other than by increasing the copy number of the gene or using a strong promoter, (5) the identity or structure of other genes related to metabolic pathways which reduce the formation of the desired L-amino acid, and (6) how to modify the genes described in (5) such that their expression is partially switched off.

As discussed previously, while one could argue that the full scope of the claimed invention is enabled since one can isolate the desired genes by structural homology using the structures disclosed in the specification and/or those of the prior art, it is noted that the state of the art as previously discussed teaches the unpredictability of accurately assigning function based on sequence homology and discloses several examples of how small structural changes can lead to major changes in function. See the teachings of Bork, Broun et al., Seffernick et al., Van de Loo et al. and Witkowski et al. already discussed. Since structure determines function, one would require some knowledge or guidance as to which are the structural elements required in a

polynucleotide to encode a protein of the desired function as well as which are the modifications required in a polynucleotide such that the corresponding protein displays amplified activity or reduced activity, as required by the claims. Also, no disclosure has been provided of which are the modifications in the regulatory elements of the recited genes that would result in reduced expression or increased expression of the desired genes, as recited in the claims. Therefore, due to the lack of relevant examples, the amount of information provided, the lack of knowledge about the critical structural elements and/or structural modifications required to obtained the desired function, and the unpredictability of the prior art in regard to function based on homology, one of ordinary skill in the art would have to go through the burden of undue experimentation in order to (1) isolate the genes, (2) determine the gene modifications required such that their corresponding gene products have increased activity or reduced activity, (3) determine which L-amino acids can be made using the large number of genes and gene modifications encompassed by the claims. Thus, Applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the invention in a manner reasonably correlated with the scope of the claims.

Claim Rejections - 35 USC § 103

25. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

26. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

27. Claims 1, 4, 5, and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Eikmanns et al. (U.S. Patent No. 6420151, filed on 12/7/1999) in view of Medina et al. (J. Bacteriol. 172(12):7151-7156, 1990; cited in the IDS), Goldie et al. (J. Bacteriol. 141(3):1115-1121, 1980; cited in the IDS), and Applicant's admission of the state of the art on page 1, lines 11-15 of the specification.

Eikmanns et al. teaches the production of L-lysine and L-threonine with a C. glutamicum strain which comprises a deletion mutation in the PEP carboxykinase gene (column 10, line 57-column 13, line 16). Eikmanns et al. does not teach the production of L-amino acids with an Enterobacteriaceae cell which comprises a deletion mutation in the PEP carboxykinase gene. Medina et al. teaches the structure of the pckA gene (Abstract, Figure 2) in E. coli (member of the Enterobacteriaceae family). Goldie et al. teaches a mutant E. coli deficient in PEP carboxykinase activity (Abstract). Neither Goldie et al. nor Medina et al. teach the production of L-amino acids.

Claims 1, 4, 5 and 9 are directed in part to a fermentation process for the production of L-lysine or L-threonine wherein an Enterobacteriaceae microorganism has been modified such that

it contains a PEP carboxykinase gene which expresses a PEP carboxykinase that has reduced or no activity.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to create a mutant E. coli comprising an inactivating deletion in the pckA gene using the nucleotide sequence disclosed by Medina et al. for the production of L-lysine or L-threonine, or use the mutant E. coli of Goldie et al. for the production of L-lysine of L-threonine, as taught by Eikmanns et al. A person of ordinary skill in the art is motivated to create such E. coli mutant for the production of L-lysine or L-threonine, or to use the E. coli mutant of Goldie et al. for the benefit of producing these amino acids since, as admitted by Applicants in page 1, lines 11-15, E. coli is a well known microorganism for the production of amino acids. Furthermore, as known in the art, its cultivation is relatively short, straightforward, and requires inexpensive media. One of ordinary skill in the art has a reasonable expectation of success at creating an E. coli mutant with an inactivating deletion in the pckA gene and use it for L-lysine or L-threonine production since Medina et al. teaches the pckA gene structure and Eikmanns et al. teaches the production of L-lysine and L-threonine with a C. glutamicum cell comprising an inactivating deletion in the pckA gene. Similarly, one of skill in the art has a reasonable expectation of success at using the E. coli mutant of Goldie et al. for L-lysine or L-threonine production since Eikmanns et al. teaches the production of L-lysine and L-threonine with a C. glutamicum cell comprising an inactivating deletion in the pckA gene. Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made.

28. Claims 2 and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Eikmanns et al. (U.S. Patent No. 6420151, filed on 12/7/1999) in view of Medina et al. (J. Bacteriol. 172(12):7151-7156, 1990; cited in the IDS), Goldie et al. (J. Bacteriol. 141(3):1115-1121, 1980; cited in the IDS), Applicant's admission of the state of the art on page 1, lines 11-15 of the specification, and further in view of Katinka et al. (Proc. Natl. Acad. Sci. 77(10):5730-5733, 1980; GenBank accession number V00361).

The teachings of Eikmanns et al., Medina et al. and Goldie et al. have been discussed above. In addition, Eikmanns also teaches that it is advantageous to overexpress one or more enzymes of the particular biosynthesis route in addition to the attenuation of the PEP carboxykinase gene such that the overexpression of the C. glutamicum dapA gene for L-lysine production and the overexpression of the homoserine dehydrogenase gene for L-threonine production (column 6, line 60-column 7, line 11). Katinka et al. teaches the nucleotide sequence of the E. coli thrA gene (part of the thrABC operon) as shown in the GenBank entry provided. Katinka et al. does not teach a method of producing L-amino acids with an E. coli cell comprising an inactivating deletion in the pckA gene and wherein said cell has been further modified such that the thrA gene is amplified.

Claim 2 is directed to the process of claim 1 as described above with the added limitation that other genes involved in the biosynthetic pathway of the desired L-amino acid can be amplified. Claim 6 is directed in part to the process of claim 1 with the added limitation that the gene encoding homoserine dehydrogenase (thrABC operon) is amplified.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to create a mutant E. coli comprising an inactivating deletion in the pckA gene of

Medina et al. wherein said mutant cell further comprises a modification such that the E. coli thrA gene is amplified using the nucleotide sequence disclosed by Katinka et al., for the production of L-lysine or L-threonine, or use the mutant E. coli of Goldie et al. and further modify it to amplify the E. coli thrA gene of Katinka et al., for the production of L-lysine of L-threonine, as taught by Eikmanns et al. A person of ordinary skill in the art is motivated to create such E. coli mutant for the production of L-lysine or L-threonine, or to use the E. coli mutant of Goldie et al. and further modify it as indicated above, for the benefit of producing these amino acids since E. coli is well known and widely used for amino acid production and also in view of the teachings of Eikmanns et al. in regard to the advantage of overexpressing other enzymes involved in the biosynthesis of the desired amino acid. One of ordinary skill in the art has a reasonable expectation of success at creating an E. coli mutant with an inactivating deletion in the pckA gene and capable of overexpressing the E. coli thrA gene for L-lysine or L-threonine production since Medina et al. teaches the pckA gene structure, Katinka et al. teaches the E. coli thrA gene structure, overexpression of E. coli genes is well known and widely used in the art, and Eikmanns et al. teaches the production of L-lysine and L-threonine with a C. glutamicum cell comprising an inactivating deletion in the pckA gene. Similarly, one of skill in the art has a reasonable expectation of success at using the E. coli mutant of Goldie et al., modify it to amplify the E. coli thrA gene, and use such mutant for L-lysine or L-threonine production since overexpression of E. coli genes is well known and widely used in the art, and further in view of the teachings of Eikmanns et al.. Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made.

Double Patenting

29. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

30. Claims 1, 3, 4, and 5 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 9-10 of copending Application No. 10/076416 (common inventors Mechthild Rieping and Georg Thierbach). An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim not is patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other. Claims 9-10 of copending Application No. 10/076416 are directed in part to a fermentation process for the production of L-amino acids which uses an Enterobacteriaceae microorganism modified such that it contains a pyruvate oxidase (poxB) gene and a PEP carboxykinase gene (pckA) wherein the expression of said genes has been reduced or

eliminated. Pyruvate oxidase is responsible for the conversion of pyruvate directly to acetate and CO_2. Claims 1, 3, 4, and 5 of the instant application are directed in part to a fermentation process for the production of L-amino acids which uses an Enterobacteriaceae microorganism modified such that it contains a PEP carboxykinase gene wherein the expression of said gene has been reduced or eliminated and wherein said microorganism further comprises a modification such that metabolic pathways which reduce the formation of the desired L-amino acid are partially switched off. Since pyruvate oxidase is part of the pathway which directs pyruvate away from amino acid biosynthesis in order to synthesize acetate and CO_2, reduction or elimination of expression of a gene encoding pyruvate oxidase would constitute a modification which partially switch off a metabolic pathway which reduces the formation of the desired L-amino acid. Therefore, claims 9-10 of copending Application No. 10/076416 would anticipate claims 1, 3-5 of the instant application as written.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

31. Claims 1, 3, 4, and 5 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 12-14 of copending Application No. 10/114043 (common inventors Mechthild Rieping and Thomas Hermann). An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim not is patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225

USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other. Claims 12-14 of copending Application No. 10/114043 are directed in part to a fermentation process for the production of L-amino acids which uses an Enterobacteriaceae microorganism modified such that it contains a deoxyglucose sensitive (dgsA or mlc) gene and a PEP carboxykinase gene (pckA) wherein the expression of said genes has been reduced or eliminated. Claims 1, 3, 4, and 5 of the instant application are directed in part to a fermentation process for the production of L-amino acids which uses an Enterobacteriaceae microorganism modified such that it contains a PEP carboxykinase gene wherein the expression of said gene has been reduced or eliminated and wherein said microorganism further comprises a modification such that metabolic pathways which reduce the formation of the desired L-amino acid are partially switched off. Since the deoxyglucose sensitive protein is a repressor of the mannose-specific EII transporter (genes manXYZ; capable of the transport of sugars such as glucose and mannose) of the PEP-dependent carbohydrate phosphotransferase system, it negatively controls the transport of sugars. As such, reduction or elimination of the expression of the dgsA gene would constitute a modification which partially switch off a metabolic pathway which reduces the formation of the desired L-amino acid since more sugar would be available for amino acid production. Therefore, claims 12-14 of copending Application No. 10/114043 would anticipate claims 1, 3-5 of the instant application as written.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

32. Claims 1, 3, 4, and 5 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 12-14 of copending

Application No. 10/114048 (common inventors Mechthild Rieping and Thomas Hermann). An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim not is patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other. Claims 12-14 of copending Application No. 10/114048 are directed in part to a fermentation process for the production of L-amino acids which uses an Enterobacteriaceae microorganism modified such that it contains an isocitrate lyase (aceA) gene and a PEP carboxykinase gene (pckA) wherein the expression of said genes has been reduced or eliminated. Isocitrate lyase is responsible for the conversion of isocitrate directly to succinate. Claims 1, 3, 4, and 5 of the instant application are directed in part to a fermentation process for the production of L-amino acids which uses an Enterobacteriaceae microorganism modified such that it contains a PEP carboxykinase gene wherein the expression of said gene has been reduced or eliminated and wherein said microorganism further comprises a modification such that metabolic pathways which reduce the formation of the desired L-amino acid are partially switched off. Since isocitrate lyase is part of the pathway which directs isocitrate away from the synthesis of α-ketoglutarate and succinyl-CoA, which are amino acid precursors, reduction or elimination of expression of a gene encoding isocitrate lyase would constitute a modification which partially switch off a metabolic pathway which reduces the formation of the desired L-

amino acid. Therefore, claims 12-14 of copending Application No. 10/114048 would anticipate claims 1, 3-5 of the instant application as written.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

33. Claims 1, 3, 4, and 5 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 12-14of copending Application No. 10/114073 (common inventors Mechthild Rieping and Thomas Hermann). An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim not is patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other. Claims 12-14 of copending Application No. 10/114073 are directed in part to a fermentation process for the production of L-amino acids which uses an Enterobacteriaceae microorganism modified such that it contains a fructose repressor (fruR) gene and a PEP carboxykinase gene (pckA) wherein the expression of said genes has been reduced or eliminated. Claims 1, 3, 4, and 5 of the instant application are directed in part to a fermentation process for the production of L-amino acids which uses an Enterobacteriaceae microorganism modified such that it contains a PEP carboxykinase gene wherein the expression of said gene has been reduced or eliminated and wherein said microorganism further comprises a modification such that metabolic pathways which reduce the formation of the desired L-amino acid are

partially switched off. The fructose repressor protein is a negative regulator of a diphosphoryl transfer protein (fruB), which is part of the fructose utilization system. Since the fructose repressor protein negatively controls fructose transport into the cell, elimination or attenuation of expression of a gene encoding the fructose repressor protein would constitute a modification which partially switch off a metabolic pathway which reduces the formation of the desired L-amino acid since more fructose would be directed for amino acid synthesis. Therefore, claims 12-14 of copending Application No. 10/114073 would anticipate claims 1, 3-5 of the instant application as written.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

34. No claim is in condition for allowance.

35. Applicants are requested to submit a clean copy of the pending claims (including amendments, if any) in future written communications to aid in the examination of this application.

36. Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (703) 308-4556. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (703) 306-0288. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (703) 308-3804. Any inquiry of

a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Delia M. Ramirez, Ph.D.
Patent Examiner
Art Unit 1652

DR
July 28, 2003

REBECCA E. PROUTY
PRIMARY EXAMINER
GROUP ~~1200~~ 1600